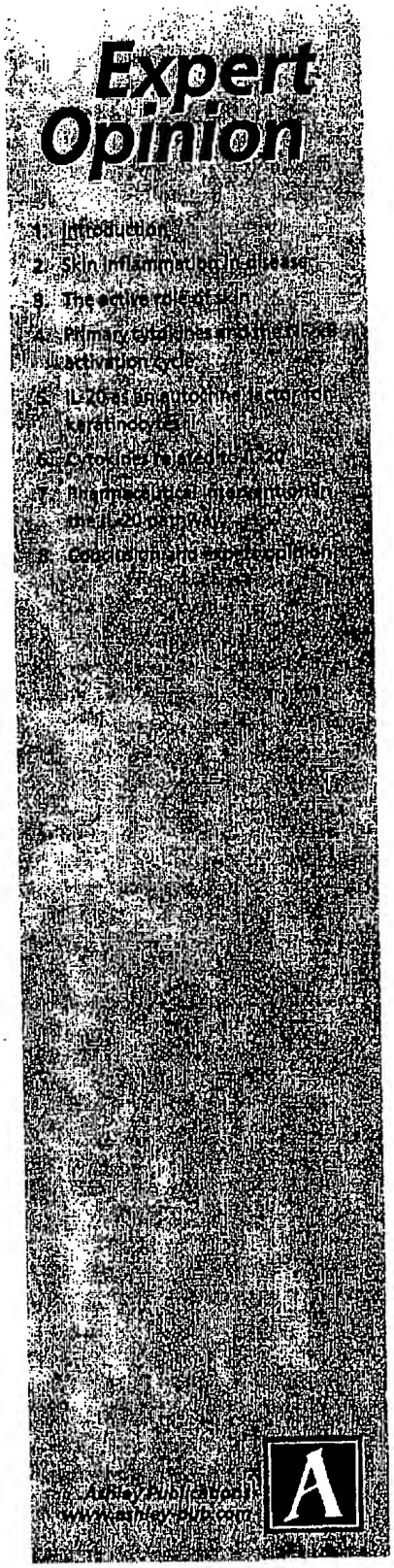

Anti-inflammatory

IL-20: a new target for the treatment of inflammatory skin disease

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The discovery of dramatic pro-inflammatory effects of IL-20 on skin highlighted a novel regulatory pathway in cutaneous inflammation. Specific receptor complexes for IL-20 are induced on keratinocytes and transmit potent signals via the signal transducer and activator of transcription-3. In response to IL-20, keratinocytes proliferate and express pro-inflammatory genes including TNF-α, which leads to activation of NF-κB. Recently, two related cytokines, IL-19 and IL-24, have been shown to trigger the IL-20 receptor, and a second receptor complex has also been found to respond to IL-20 and IL-24. IL-20 signalling appears to be a prominent component of cutaneous inflammation, but the extent to which inflammatory processes rely upon it is unknown. Nonetheless, the prevalence of diseases involving pathological cutaneous inflammation makes the identification of safe and effective anti-inflammatory therapies for the skin a priority. Detailed understanding of the signal transduction pathways by which the skin responds to IL-20 and related factors may make it possible to develop new pharmaceutical agents to selectively suppress cutaneous inflammation.

Keywords: cytokine, epidermis, IL-19, IL-20, IL-22, IL-24, IL-26, inflammation, keratinocyte, receptor, skin, signal transducer and activator of transcription-3 (STAT-3)

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1. Introduction

Coordination of the action of cells and tissues of multicellular organisms requires cell–cell communication. One of the prominent mechanisms by which cells transmit signals to other cells is by the release of molecules, including soluble proteins known as cytokines, which bind to specific receptors and provoke changes in target cells. Some of these signalling events are associated with developmental or homeostatic processes while others are part of reactive immune responses. A number of disease conditions involve inappropriate or excessive inflammatory reactions. An understanding of the molecular mechanisms of these reactions can lead to the development of hypothesis-based interventions. The characterisation of IL-20 and the discovery of its potent effects on keratinocytes has revealed a new regulatory circuit contributing to cutaneous inflammation. More recently, IL-19 and IL-24 have been shown to engage and activate the IL-20 receptor, and a second receptor complex that responds to IL-20 and IL-24 has been identified. In this review, the signalling pathways of IL-20 and related cytokines will be examined in the context of the normal biology and pathological reactions of the skin.

2. Skin inflammation in disease

The skin is the largest and most visible organ of the body, and its health is both a critical component of quality of life and an important gauge of overall health. In addition

...effects, the emotional toll of chronic dis... changes in appearance and disfigurement caused ... disorders, can be very heavy. The prevalence of ...disorders and the imperative to control them combine to create a significant demand for effective interventions.

Many of the pathological conditions of the skin are caused by inflammatory reactions of the immune system. The most frequent skin disorders, dermatophytoses and acne, involve inflammatory responses provoked by pathogens (fungi and bacteria, respectively). Inflammation associated with these conditions subsides when the infection is controlled by antibiotics or prevented by altering the behaviour of sebaceous glands. Several other skin disorders involving inflammation of unknown aetiology affect as many as 5% of the US population. These include seborrheic dermatitis, atopic dermatitis and psoriasis. Of these, expenditures on medications to treat psoriasis are disproportionately high, largely because of its persistence and resistance to treatment [1].

Psoriasis is a disorder that presents as patches of crusty scales over glossy reddened skin. The most prominent feature of psoriasis is the hyperproliferation and perturbed differentiation of epidermal keratinocytes leading to accumulation of scales. Abnormal angiogenesis and infiltration of inflammatory T_{H1} cells expressing IFN-γ are also evident. In the past, the epidermal hyperproliferation has been ascribed to cell-autonomous defects in the keratinocytes. More recently, it has become clear that activation of T cells is a critical component of the pathogenic process. Several biological agents that target pathogenic T cells have been found to be effective in controlling psoriasis. These include an anti-CD4 monoclonal antibody [2,3], an IL-2 diphtheria toxin fusion protein [4], an anti-CD11a monoclonal antibody [5], and a fusion protein consisting of lymphocyte function-associated antigen-3 (LFA-3) and the Fc domain of immunoglobulin [6]. The therapeutic effects of the potent immunosuppressive drugs cyclosporin A [7] and FK506 (tacrolimus) [8] in the treatment of psoriasis have been known for some time. While these drugs are best known for their effects on T cells, they have also been demonstrated to act directly on keratinocytes [9-11].

In contrast to psoriasis, atopic dermatitis (also known as atopic eczema) is an allergic disorder that frequently arises in individuals who have, or will develop allergic rhinitis or constrictive airway disorders (asthma). Atopic dermatitis is associated with elevated levels of IgE and enhanced expression of T_{H2} cytokines IL-4, IL-5 and IL-13. It involves chronic activation and degranulation of mast cells and vascular permeability leading to oedema.

Thus, psoriasis exhibits features of a cell-mediated Type 1 immune reaction, while atopic dermatitis more closely resembles a humoral or Type 2 immune reaction.

3. The active role of skin

3.1 Differentiation versus proliferation in the epidermis

As the interface with the outside world, the primary function of the skin is to act as a protective barrier. It keeps foreign material out of the body and keeps moisture in. The epidermis maintains the barrier by undergoing a continuous process of regeneration in which proliferation of the basal layer of keratinocytes adjacent to the dermis pushes cells out to the surface as they differentiate and die. The precipitated structural proteins of the cells (keratins), interspersed with the hydrophobic components of the membranes, adhere together to form the impermeable barrier known as the stratum corneum. As these cornified cells are broken loose by abrasion, they are replaced by new cells from below.

The structure of the epidermis is determined by this homeostatic balance of proliferation, differentiation and sloughing. Perturbations in the behaviour of keratinocytes can have a dramatic impact on the health of skin. Enhanced keratinocyte proliferation can result in a significant thickening of the epidermis termed acanthosis. Excessive proliferation also pushes some keratinocytes up into the stratum corneum before they fully differentiate. This phenomenon, called parakeratosis, is characterised by defects in the barrier function and retention of nuclear remnants in the stratum corneum.

Understanding the mechanism by which a keratinocyte decides between differentiation and further proliferation is an important goal of cutaneous research. During development and wound repair, this balance is affected by signals transmitted from the dermis [12-14]. This balance is also affected by inflammation, and IL-20 may be a signal originating from within the epidermis that contributes to this decision.

3.2 Keratinocyte activation

The secondary function of the skin is to interact with the immune system. The epidermis acts as a sensor for pathogenic and traumatic challenges. In response to those challenges, it transmits pro-inflammatory signals to other resident cutaneous cells as well as more mobile cells of the haematopoietic immune system. Certain stimuli have direct effects on keratinocytes and underlying fibroblasts causing them to release cytokines that trigger the innate immune system. The ability of keratinocytes to release complex arrays of pro-inflammatory factors when provoked by stimuli such as physical trauma, ultraviolet irradiation, bacterial products or cytokines, allows them to recruit inflammatory cells and regulate their behaviour.

Factors released by keratinocytes in response to various stimuli include: TNF-α, IL-1α, IL-3, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, TGF-α, TGF-β, IFN-γ and monocyte chemotactic protein-1 (MCP-1), among others [15]. Although it is not yet clear under which circumstances keratinocytes express IL-20, it appears that it should now also be included in this list. These factors convey signals in a paracrine fashion to other cells including leukocytes, endothelial cells, fibroblasts and adjacent keratinocytes as well as in an autocrine fashion to the activated cells themselves. As discussed below, TNF-α, IL-1α, and IL-18 are three prominent autocrine factors that are important for amplifying and sustaining the activated state of the keratinocytes; they also

transmit signals to many other types of cells. IL-20 appears to be both an autocrine and paracrine factor that amplifies and sustains keratinocyte activation.

Other stimuli, such as antigenic challenges, are mediated by cells of the acquired immune system. Foreign antigens are captured and processed by antigen-presenting cells (APCs) and carried to lymphoid tissue where they activate antigen-specific T cells. Antigen-specific T cells migrate into the tissue where they encounter more antigen and become further activated. Products released by activated T cells convey signals to keratinocytes. IFN-γ, produced by T_{H1} cells, stimulates keratinocytes to express intercellular adhesion molecule-1 (ICAM-1), which facilitates adhesion to lymphocytes, and IL-7, which supports viability of T cells. Therefore, in addition to transmitting signals to recruit and activate effector cells, the epidermis undergoes changes to provide a supportive environment for the immune system as it repels pathogens.

4. Primary cytokines and the NF-κB activation cycle

TNF-α, IL-1 and IL-18 have been called primary cytokines because binding to their cognate receptors results in the activation of the transcription factor NF-κB, which in turn activates genes encoding a broad array of pro-inflammatory products [16]. In the absence of activating signals, NF-κB resides sequestered as an inactive form in the cytoplasm bound tightly to a specific inhibitory molecule, Iκβ. Signals transmitted by the primary cytokine receptors lead to degradation of Iκβ and release of the active form of NF-κB. Activated NF-κB translocates to the nucleus where it promotes transcription of IL-1, TNF-α and other pro-inflammatory genes including cellular enzymes, adhesion molecules, chemokines and cytokines. This self-enhancing circuit is a central mechanism in the cellular inflammatory response that provides for prolonged and enhanced activation of the array of genes associated with inflammation (Figure 1).

The NF-κB activation circuit can be triggered by exposure to bacterial products [17], physical stresses such as osmotic shock or ultraviolet irradiation, which directly activate the epidermal growth factor (EGF), TNF and IL-1 receptors [18], or trauma, which releases intracellular stores of preformed IL-1α [19]. The ability of glucocorticoids to inhibit the activation and action of NF-κB contributes to their broad anti-inflammatory properties [16,20]. Recently developed antagonists of the TNF-α [21] and IL-1 [22] receptors also exert potent anti-inflammatory effects by disrupting the NF-κB activation cycle.

The discovery that signalling by the IL-20 receptor activates the TNF-α gene in keratinocytes identifies a previously unknown mechanism of initiating the NF-κB activation circuit. While the activation of NF-κB by increased expression of TNF-α is likely to contribute to the dramatic phenotype of IL-20 transgenic mice, the normal biological circumstances in which this is relevant are unclear [23].

5. IL-20 as an autocrine factor for keratinocytes

IL-20 was initially identified as a mRNA expressed in keratinocytes that is related to IL-10 and contains instability sequences in it's 3′ untranslated region [23]. The relevance of IL-20 to the skin was first appreciated when several transgenic mice were generated with a cDNA encoding IL-20 driven by various promoters. Each of these mice were runted, had abnormally tight and shiny skin and died within days of birth. The epidermis of the transgenic mice was found to be profoundly thickened and had increased numbers of keratinocytes. Moreover, expression of certain markers of differentiation and proliferation, which are normally confined to the basal layer, was detected in the suprabasal layers of the epidermis. These include proliferating cell nuclear antigen (PCNA) and keratins-5, -6 and -14 [23]. These perturbations appeared to have been caused by circulating IL-20, since the phenotype was observed in mice that expressed the transgene in tissues other than skin, such as in the liver from the albumin promoter, as well as in mice with a transgene directed to skin.

The profound effects of IL-20 on the epidermis of the transgenic mice, and the fact that IL-20 was found to be expressed by keratinocytes, focused attention on IL-20 as an autocrine factor for keratinocytes. Exposure of an immortalised keratinocyte cell line (HaCaT) to IL-20 was found to activate signal transducer and activator of transcription-3 (STAT-3), one of the transcriptional activators involved in IL-10 signalling [23]. Numerous different signalling molecules can activate STAT-3 in several different cell types [24]. Activated STAT-3 translocates to the nucleus and stimulates transcription of several STAT-responsive genes. The central importance of STAT-3 is demonstrated by the observation that STAT-3-deficient mice die as early embryos. Specific deletion of the STAT-3 gene in keratinocytes blocks their responses to EGF, hepatocyte growth factor (HGF) and IL-6 [25]. Although STAT-3-deficient keratinocytes form relatively normal skin, they are defective in wound healing and have altered secondary hair cycles. While EGF is clearly an important cytokine for keratinocytes, it is possible that some of the deficits in STAT-3-deficient keratinocytes are also due to their inability to respond to IL-20. IL-10 signal transduction includes both STAT-3-dependent and -independent pathways [26]. Therefore, it is possible that IL-20 signal transduction may also utilise multiple pathways. As discussed below, two different receptor complexes are triggered by engagement of IL-20, but each of these activates STAT-3 [27].

6. Cytokines related to IL-20

6.1 Genetics

IL-20 is one of at least a dozen cytokines related to IL-10 [28]. Six members of the IL-10 family are encoded by genes at two loci in the human genome. Genes coding for IL-10, IL-19, IL-20 and IL-24 (formerly melanoma differentiation-associated

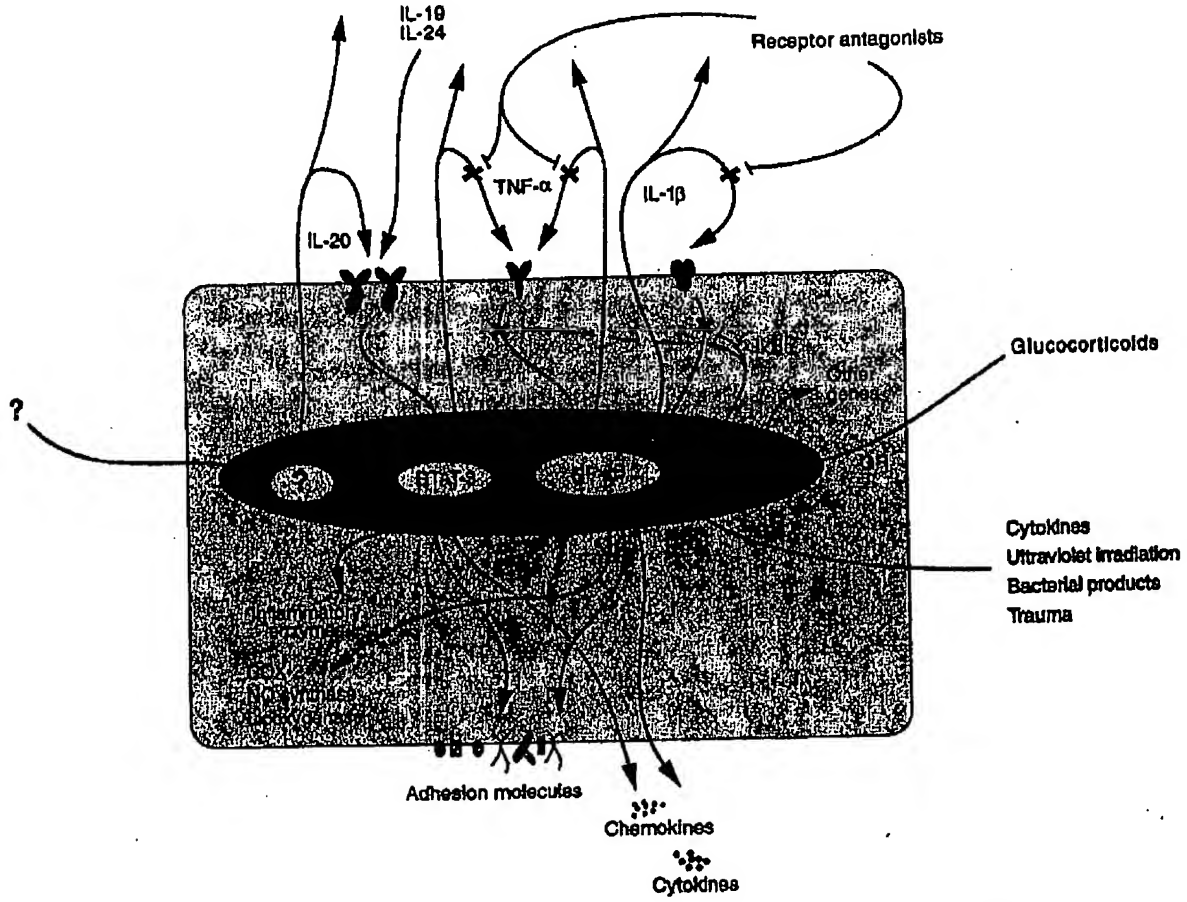

Figure 1. IL-20 and NF-κB activation in keratinocytes. Engagement of the TNF-α and IL-1 receptors activates NF-κB, which in turn stimulates further expression of IL-1 and TNF-α and an array of other pro-inflammatory genes. This amplification cycle can be triggered by direct stimuli, such as bacterial products, ultraviolet irradiation or trauma, which releases intracellular stores of preformed IL-1. IL-20 also contributes to the activation of NF-κB by turning on TNF-α and other pro-inflammatory genes. IL-1 further enhances the sensitivity of keratinocytes to IL-20 and amplifies their response to it. Glucocorticoids exert their broad immunosuppressive effects by altering the expression of numerous genes including upregulation of IκBα, which blocks the activation and action of NF-κB, and downregulation of NF-κB itself. IL-1 and TNF-α receptor antagonists diminish NF-κB activation by competing for extracellular ligands.
COX: Cyclooxygenase; GR: Glucocorticoid receptor; NO: Nitrogen oxide; STAT: Signal transducer and activator of transcription.

gene-7 [MDA-7], mob-5, IL-4-induced secreted protein [FISP], C49a, respectively) are clustered on chromosome 1 near position 1q32 [23,29,30], while the genes coding for IL-22 and IL-26 (formerly IL-10-related T cell-derived inducible factor [IL-TIF] and AK-155, respectively) are near one another in the vicinity of the gene for IFN-γ on chromosome 12 at position 12q15 [31,32]. It is clear that these genes evolved from a common ancestor, and the fact that they are found clustered together may indicate that they have evolved relatively recently by duplication events. Interestingly, the murine IL-22 gene, which is also close to the IFN-γ gene, is duplicated in some strains of mice [32].

At least seven other IL-10-related cytokines are encoded by various viral genomes [28]. The presence of these IL-10-related genes in viral genomes is a clear indication that their bioactivities as agonists (engaging and triggering cognate receptors) or antagonists (non-signalling competitive inhibitors), confer competitive advantages to the viruses, most likely by interfering with host immunity. The ability of IL-10 to reign in inflammatory immune responses is also exploited by certain intracellular bacteria. While they do not produce their own versions of IL-10, they provoke expression of high levels of endogenous IL-10 by host cells [33].

6.2 Biological activities

While some constitutive expression of IL-10, IL-19 and IL-24 has been detected, the IL-10 family of cytokines are principally

expressed in response to activating stimuli. The six IL-10-related cytokines encoded by the human genome are produced by different cells in response to various stimuli, and appear to have diverse biological roles.

IL-10 is a product of certain activated T cells, B cells, monocytes and keratinocytes, and diminishes activation and effector functions of T cells, monocytes and macrophages while promoting the production and function of T_{H2} and regulatory T cells. The biology of IL-10 has been studied extensively and is reviewed elsewhere [34].

IL-19 is a product of B cells and monocytes stimulated with lipopolysaccharide (LPS) or granulocyte macrophage colony-stimulating factor (GM-CSF) [30,35]. Exposure of monocytes to IL-19 induces them to release IL-6 and TNF-α, produce reactive oxygen compounds, and undergo apoptosis [36]. In contrast to IL-20, transgenic mice expressing IL-19 are reported to lack any obvious cutaneous pathology [37].

IL-22 is produced by T cells and natural killer (NK) cells in response to IL-9, and elicits an acute phase response from the liver [38-40] and inflammatory changes in the pancreas [41]. Structural analysis of IL-22 reveals that it is distinct from IL-10, and suggests that it may be active as a monomer [42].

IL-24 was originally identified as an autocrine differentiation factor regulated by ras and mitogen-activated protein kinase (MAPK) in melanoma cells [43,44]. It is also produced in healing wounds [50], activated T_{H2} cells [51], peripheral blood mononuclear cells activated by concanavalin A [52], LPS or phytohaemaglutination antigen [53], and macrophages in response to LPS and IL-4, or infection by influenza virus [54]. The ability of IL-24 to induce apoptosis in malignant cells [45,46] has prompted efforts to develop it as a therapeutic anticancer agent [47-49].

IL-26 was identified as a secreted product of T cells, transformed by *Herpesvirus saimiri*, which has structural homology with IL-10, and is encoded by a gene in close proximity to the IL-10, IL-19 and IL-20 genes [31,32,55]. No bioactivities or cognate receptors for IL-26 have been described.

6.3 Receptors and signal transduction

To date, five of the six human IL-10-related cytokines have been shown to engage and trigger one or more of four different dimeric receptor complexes with shared chains. Figure 2 depicts cellular sources and models of the known receptor complexes and signalling pathways for the IL-10 family of cytokines. Like their cognate ligands, expression of the IL-20Rα and IL-20Rβ chains are strongly induced by cellular activation, and they are only detected on keratinocytes, endothelial cells and certain monocytes in association with inflammatory conditions such as psoriasis [23]. As shown in Figure 2, IL-20 and IL-24 can each bind and trigger both the IL-20Rα/IL-20Rβ and the IL-22Rα/IL-20Rβ complexes, while IL-19 only activates the IL-20Rα/IL-20Rβ complex [23,27,37,52]. Engagement of each of these receptor complexes results in the activation of STAT-3 by phosphorylation [23,27,37].

IL-22 engages a receptor consisting of IL-22Rα and IL-10Rβ, which activates Janus kinase-1 (JAK-1) and tyrosine kinase-2 (TYK-2) leading to STAT-1, STAT-3 and STAT-5 phosphorylation and translocation [38-40]. IL-22 signal transduction is similar to IL-10 in that it involves activation of JAK-1 and TYK-2, but it is distinct in that it also activates components of the MAPK pathways that are not activated in response to IL-10. IL-22 signalling also results in phosphorylation of Ser 727 of STAT-3, a feature of IL-6 signal transduction that is not found in IL-10 signalling [56].

7. Pharmaceutical intervention in the IL-20 pathway

7.1 The utility of blocking IL-20 signalling

The response of the epidermis to inflammatory processes contributes to the underlying pathology of many skin diseases. A number of potent drugs with broad immunosuppressive effects, such as corticosteroids, fusion toxins or receptor antagonists, are currently available, and are effective in controlling the symptoms of these disorders, although the adverse consequences of systemic immunosuppression often limit or preclude their clinical use.

Three observations point towards a central role for IL-20 and related cytokines in the regulation of cutaneous inflammation and the ensuing pathological epidermal changes:

- The profound effects of IL-20 expression in transgenic mice.
- The expression of the IL-20R chains in psoriasis.
- The pro-inflammatory effects of IL-20 on keratinocyte gene expression.

The apparently specialised role of IL-20 signalling in cutaneous tissue may present an opportunity to create pharmaceutical interventions that selectively mitigate inflammatory processes in the skin while sparing inflammation in other tissues.

To evaluate prospects for inhibiting biological responses to IL-20, it is helpful to consider our current understanding of the stepwise events involved. IL-20 expression is regulated by unknown mechanisms: released IL-20 diffuses to engage receptors on recipient cells; bound receptors undergo changes that promote activity of cytoplasmic JAK kinases; and cytoplasmic kinases phosphorylate STAT molecules, which then translocate to the nucleus and initiate transcription of certain responsive genes. Biochemical intervention may be possible at one or more components in each of these stages, but only a few approaches have been successful to date.

7.2 Endogenous regulators of signal transduction

Several extracellular and intracellular mechanisms of negative regulation of signalling of various cytokines have been identified. Certain soluble isoforms or homologues of receptors act as binding proteins, scavenging certain cytokines and inhibiting them from binding cell-bound signalling receptors. Consistent with this paradigm, a soluble protein related to the

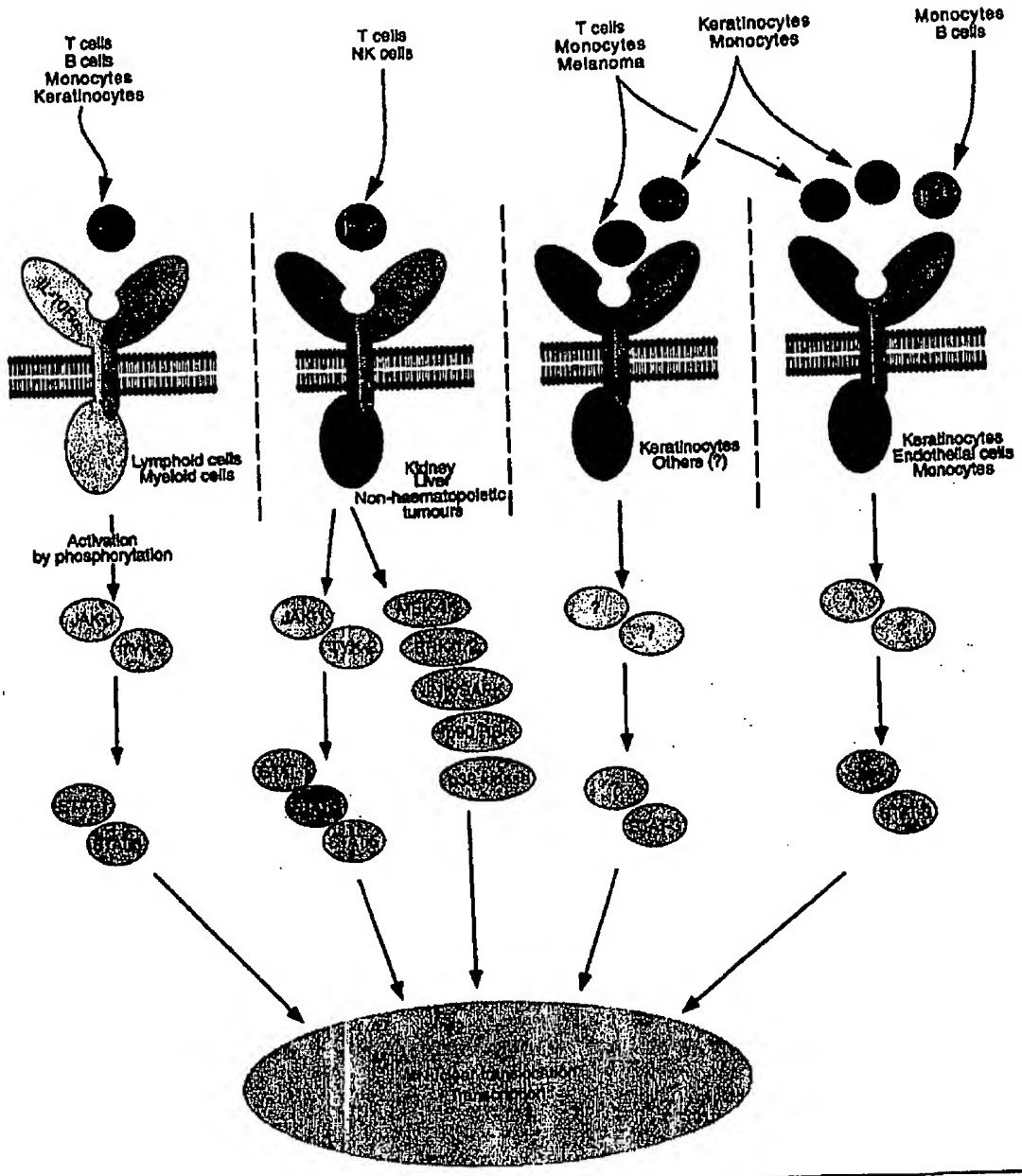

Figure 2. IL-10 family of cytokines and their cognate receptors. Cytokines of the IL-10 family are produced by several different cell types in response to stimuli. Four different receptor complexes, expressed by various cell types, transmit signals in response to cytokines of the IL-10 family. Each complex consists of two transmembrane polypeptides, a larger α-chain with a prominent cytoplasmic domain and a smaller β-chain with a minimal cytoplasmic domain. Upon engagement, the receptor complexes activate JAK proteins, which in turn activate STAT proteins. Activated STATs translocate to the nucleus and regulate transcription of genes. IL-22 has also been shown to activate components of the MAPK signalling pathway and stimulate a serine phosphorylation of STAT-3.

ERK: Extracellular signal-regulated kinase; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MEK: Mitogen-induced extracellular kinase; NK: Natural killer; RSK: Ribosomal S6 kinase; SAPK: Stress-activated protein kinase; STAT: Signal transducer and activator of transcription; TYK: Tyrosine kinase.

IL-22 receptor has been described and demonstrated to inhibit the action of IL-22 *in vitro* [57,58].

Eight suppressors of cytokine signalling (SOCS) proteins have been identified that are expressed in response to various cytokines. SOCS proteins are negative regulators of JAK kinases that inhibit their kinase activities and accelerate their ubiquitination and degradation [59]. Protein inhibitors of activated STATs (PIASs) provide another level of regulation of cytokine signalling [60].

It is likely that IL-20 signalling is regulated by some or all of these mechanisms, which may present opportunities for engineering therapeutic inhibitors.

7.3 Modified receptor proteins and antibodies

Of the endogenous mechanisms of controlling cytokine signalling, only extracellular competitive inhibitors constructed from soluble versions of cognate receptors or monoclonal antibodies have been used successfully. The most notable of these are soluble versions of the TNF and IL-1 receptors, as discussed above. Therefore, soluble forms of the IL-20 and IL-24 receptors and monoclonal antibodies are probably the most specific and readily available prospects for blocking the effects of IL-20.

7.4 Small molecule kinase inhibitors

While the specific roles of the various JAK and STAT molecules in IL-20 signal transduction remain to be fully understood, advances in the biochemistry and structure of protein kinases and methods of drug discovery continue to lead to highly selective and effective inhibitors with favourable pharmacokinetics [61-65]. The recent success of the ABL (cellular homologue of Abelson virus kinase) kinase inhibitor STI-571 (imatinib mesylate, Gleevec™, Novartis) in controlling certain myeloid and lymphoid leukaemias demonstrates the promise of this approach [66]. The IL-20 signalling apparatus utilises JAK and STAT molecules that are also necessary for other essential signalling pathways [67]. STAT-3 and JAK-1 are required for signalling in response to IL-10 and IFNs [24,68] and it is likely that they are also required for IL-20 signalling. They are also critical for other important processes, as demonstrated by the fact that STAT-3-deficient mice die as early embryos [69] and JAK-1-deficient mice die soon after birth, probably as a result of aberrant neurological development caused by deficient LIF (leukaemia inhibitory factor) and CNTF (ciliary neurotrophic factor) signalling [70]. TYK-2 is activated in response to IL-10 and IL-22 and perhaps also by IL-20. TYK-2 does not appear to be essential for IL-10 signal transduction, since cells from TYK-2-deficient mice are able to respond normally to IL-10 [71]. Thus, JAK-1 is the kinase most likely to be an effective target for blocking IL-20 signalling, although it may lead to undesirable side effects.

7.5 Ligand–toxin fusion proteins

The highly specific high-affinity interaction between cytokines and their cognate receptors has been exploited to create selective cytotoxic fusion proteins that kill cells bearing the receptors. The most established of these is the IL-2 diphtheria toxin, denileukin diftitox (Ontak®, Ligand Pharmaceuticals, Inc.), for the treatment of psoriasis [4] and cutaneous T cell lymphoma [72]. This approach is best suited to circumstances in which the targeted cognate receptor is only expressed by the pathological cells, as appears to be the case for the IL-20 receptor in psoriasis. On the other hand, killing large numbers of the activated keratinocytes might significantly compromise the skin and impair wound healing.

7.6 Gene expression modifiers

Several schemes have been devised for diminishing the expression of specific genes, including the use of antisense molecules [73] and RNA interference [74]. Agents such as these that target expression of ligands (IL-19, IL-20 and IL-24) or receptors (IL-20α, IL-20β and IL-22α) might be effective in controlling cutaneous inflammation. Conversely, selectively increasing expression of SOCS or PIAS genes in basal keratinocytes or other responsive cells might also diminish IL-20 signalling.

8. Conclusion and expert opinion

The engagement of the IL-20 receptor on keratinocytes has been demonstrated to provoke skin pathology. Although the specific role of IL-20 in inflammation remains uncertain, it appears likely that its expression in keratinocytes participates in the initiation and perpetuation of the NF-κB activation circuit. Furthermore, the expression of ligands for the IL-20 and IL-24 receptors by activated monocytes and some lymphocytes may constitute a previously unknown connection between the haematopoietic immune system and the epidermis. Therefore, the relatively specialised role of IL-20 signalling in cutaneous inflammation may present opportunities for selective therapeutic intervention in cutaneous inflammatory disorders.

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